PRINCIPLES AND PRACTICE OF

INFECTIOUS DISEASES

THIRD EDITION

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175. CLASSIFICATION OF STREPTOCOCCI

ALAN L. BISNO

Streptococci are spherical or ovoid bacteria that grow in pairs or chains of varying lengths. Most are facultatively anaerobic, although some are obligate anaerobes. Streptococci are gram-positive, non-spore forming, catalase-negative, and ordinarily nonmotile. They have complex but variable nutritional requirements. Taxonomically, these organisms belong to the genus *Streptococcus*, of which there are over 20 identified species.[1] Some of these species are pathogenic for humans, most notably *Streptococcus pyogenes* and *Streptococcus pneumoniae*.

No single system of classification suffices to differentiate this heterogeneous group of organisms. Instead, classification depends on a combination of features including patterns of hemolysis observed on blood agar plates, antigenic composition, growth characteristics, biochemical reactions, and, more recently, genetic analyses.

When streptococci are cultivated on blood agar plates, notable differences in the surface morphologic characteristics (e.g., colony size, opacity) among individual strains are evident. Moreover, colonies of certain strains are surrounded by clear colorless zones within which the red cells in the medium have been completely lysed (Fig. 1). This pattern is designated β-hemolysis and is of considerable importance since it is exhibited by *S. pyogenes* and many of the other streptococci pathogenic for humans. A second group of organisms produces partial or α-hemolysis. Careful observation of α hemolytic strains under the microscope reveals an inner zone of unhemolyzed cells and an outer zone of hemolysis. α-Hemolytic colonies also produce a greenish discoloration in the medium. This greening reaction, which varies with the type of blood in the medium and the duration of incubation, gives rise to the term *viridans streptococci*, frequently applied to α-hemolytic strains. Pneumococci are α-hemolytic, as are many of the other streptococcal strains that normally inhabit the upper respiratory and gastrointestinal tract of humans. Finally, the term γ-hemolysis has been used to designate strains producing no hemolysis, although the term *nonhemolytic streptococci* is to be preferred.

More precise identification of the β-hemolytic streptococci was accomplished by Lancefield[2] who succeeded in differen-

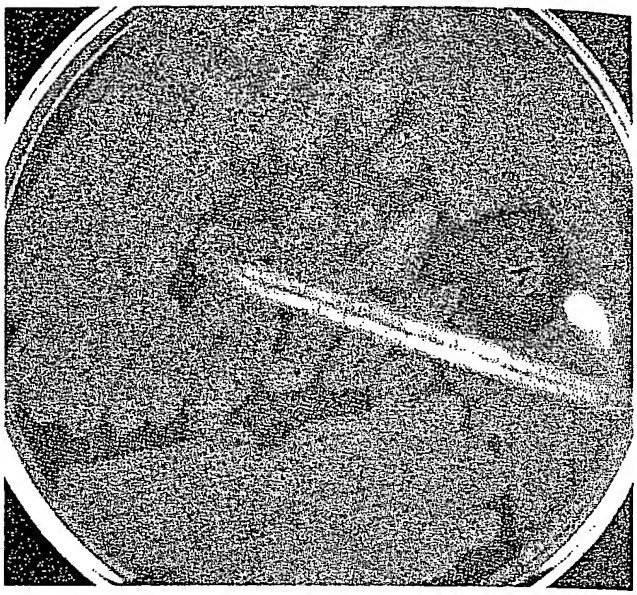

FIG. 1. Group A streptococci growing in pure culture on a sheep blood agar plate. Individual colonies are surrounded by zones of complete (β) hemolysis. Subsurface hemolysis (agar stab) is due in part to the action of streptolysin O, which is oxygen labile. The zone of inhibition around a low-potency bacitracin disk is a presumptive test for group A organisms.

TABLE 1. Streptococcal Serogroups Most Frequently Involved in Human Disease

Serogroup	*Group Specific Cell Wall Antigen*	*Usual Clinical Features*
A	Rhamnose-*N*-acetylglucosamine polysaccharide	Pharyngitis, tonsillitis, otitis media, sinusitis, scarlet fever, erysipelas, cellulitis, impetigo, pneumonia, endometritis, septicemia Delayed nonsuppurative sequelae: acute rheumatic fever, acute glomerulonephritis
B	Rhamnose-glucosamine polysaccharide	Chorioamnionitis, puerperal sepsis, neonatal sepsis and meningitis
C	Rhamnose-*N*-acetylgalactosamine polysaccharide	Upper respiratory infections
D	Glycerol teichoic acid	Genitourinary tract infections, wound infections, endocarditis
G	Rhamnose-galactosamine polysaccharide	Upper respiratory infections, cellulitis, septicemia, deep-tissue infections

tiating these organisms into serogroups by means of antigenic differences in cell wall carbohydrates. Group-specific antigens are readily extracted from streptococcal cell walls and identified by precipitin reactions using specific antisera. To date, serogroups A to H and K to V have been designated. Groups A, B, C, D, and G are those most commonly found in humans (Table 1); groups E, L, P, U, and V are isolated from humans rarely if at all.

Although the Lancefield grouping system was initially devised for the identification of β-hemolytic streptococci, certain α-hemolytic and nonhemolytic strains also contain group-specific antigen. Notable among these are group D streptococci, including the so-called enterococci, most strains of which fail to exhibit β-hemolysis. It has recently been proposed, however, that the enterococci be recognized as a separate genus.[3] The enterococci, which are significant causes of human disease, are discussed in detail in Chapter 179.

Streptococci that lack a recognizable group antigen are identified by physiologic tests that include fermentation reactions, growth at 10°C and 45°C, and growth in broth containing a high salt content. Three species of anaerobic streptococci and three species of microaerophilic streptococci are recognized in the most recent revision of *Bergey's Manual*. Hemolytic reactions of the organisms are variable. No satisfactory method of classification has been devised. These organisms are at times associated with human infections, particularly infections occurring in necrotic tissues (see also Chapter 224).

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176. STREPTOCOCCUS PYOGENES

ALAN L. BISNO

Streptococcus pyogenes (group A streptococcus) is one of the most important bacterial pathogens of humans. This ubiquitous organism is the most frequent bacterial cause of acute pharyngitis, and it also gives rise to a variety of cutaneous and systemic infections. Its unique place in medical microbiology stems from its propensity to initiate two nonsuppurative sequelae: acute rheumatic fever (ARF) and poststreptococcal acute glomerulonephritis (AGN). The former malady has been responsible for suffering, disability, and mortality in all parts of the world.

HISTORY

Streptococci were demonstrated in cases of erysipelas and wound infections by Billroth in 1874 and in the blood of a patient with puerperal sepsis by Pasteur in 1879. Fehleisen, in 1883, isolated chain-forming organisms in pure culture from erysipelas lesions and then demonstrated that these organisms could induce typical erysipelas in humans. Rosenbach applied the designation *Streptococcus pyogenes* to these organisms in 1884. Nevertheless, a variety of other appellations, now obsolete, such as *Streptococcus erysipelatos, Streptococcus scarlatinae*, and *Streptococcus hemolyticus* were applied from time to time.

Initial progress toward a rational classification of streptococci dates from the description by Schötmuller in 1903 of the blood agar technique for differentiating hemolytic from nonhemolytic streptococci. In 1919 J. H. Brown[1] made a systematic study of patterns of hemolysis and introduced the terms α-, β-, and γ-hemolysis (see Chapter 175).

Lancefield's classification of β-hemolytic streptococci into distinct serogroups in 1933[2] was a major turning point in our understanding of the epidemiology of streptococcal infections. Most strains pathogenic for humans were found to belong to serogroup A (*S. pyogenes*). Systems of serotyping group A streptococci were developed on the basis of M-protein precipitin reactions (Lancefield) or T-protein agglutination reactions (Griffith). In addition, Lancefield established the critical role of M protein in streptococcal virulence and the type-specific nature of protective immunity to group A streptococcal infection. Studies by Dochez and collaborators and by the Dicks in the 1920s established the relationship of scarlet fever to hemolytic streptococcal infection. A few years later, Todd's description of the method for titration of anti-streptolysin O (ASO) in serum added still another important tool to the armamentarium available for study of the immunology and epidemiology of streptococcal disease. Such tools were used by a number of investigators including Coburn, Collis, Rammelkamp, Stollerman, and Wannamaker to establish the relationship of group A streptococcal infection to ARF and AGN. Much of our modern knowledge of the detailed epidemiology of streptococcal infections and of ARF derives from the pioneering studies performed at Warren Air Force Base, Wyoming, during the years 1949–1951 by Rammelkamp, Wannamaker, and Denny.[3–5]

DESCRIPTION OF THE PATHOGEN

Group A streptococci grow as spherical or ovoid cells 0.6–1.0 μm in diameter and occur as pairs or as short to moderate-sized chains in clinical specimens. When growing in broth media enriched with serum or blood, long chains are frequently formed, and many strains produce capsules of hyaluronic acid. The organisms are gram-positive, nonmotile, non-spore forming, catalase-negative, and facultatively anaerobic. Group A streptococci are nutritionally fastidious and are usually cultivated in complex media, often supplemented with blood or serum.

When cultivated on blood agar plates, *Streptococcus pyogenes* appears as white to gray colonies 1 to 2 mm in diameter surrounded by zones of complete ("β") hemolysis. (Strains that fail to produce surface hemolysis occur but are rare.) Strains that produce copious amounts of the hyaluronate capsular material appear mucoid, at times resembling a water drop on the plate. Less mucoid strains assume a crinkled, so-called *matt* appearance. Small opaque colonies of organisms that lack capsules and detectable M protein are termed *glossy*.

A large number of somatic constituents and extracellular products of group A streptococci have been identified. The most important of these are indicated in the following sections.

Somatic Constituents

Figure 1 is a schematic representation of the group A streptococcal cell. The organism is enveloped in a hyaluronic acid capsule that serves as an accessory virulence factor in retarding phagocytosis by polymorphonuclear leukocytes and macrophages of the host. The cell wall is a complex structure containing many different antigenic substances. The group-specific carbohydrate of group A strains is a dimer of rhamnose and *N*-acetylglucosamine in a ratio of approximately 2:1. The mucopeptide (peptidoglycan) layer provides rigidity to the cell wall; it is composed of polymers of repeating subunits of *N*-acetyl-

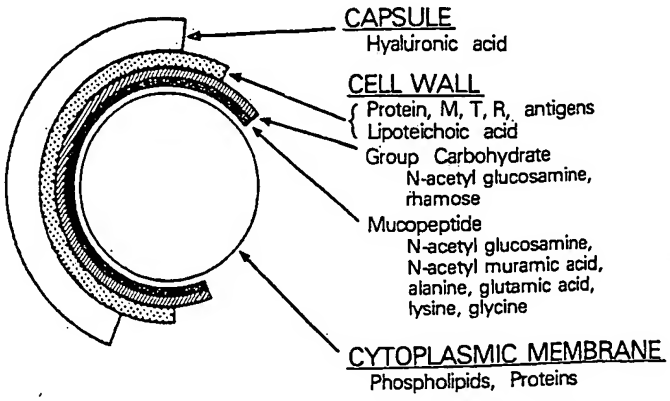

FIG. 1. Schema of group A streptococcal cell indicates somatic constituents of major biologic interest. (Modified from Krause,[6] with permission.)

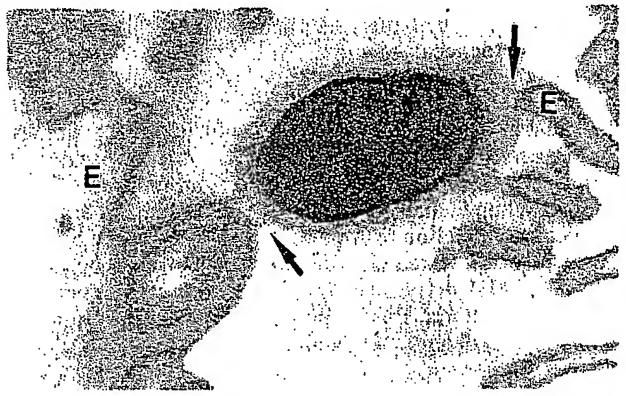

FIG. 2. Electron micrograph of group A streptococcus. Surface fibrils contain type-specific, antiphagocytic epitopes of M protein. Fibrils also participate in attachment of the streptococcal cell to the membrane (arrows) of a human oral epithelial cell (E). (×67,500) (From Beachey EH et al.,[8] with permission.)

glucosamine and *N*-acetylmuramic acid connected by amino acid side chains.

M protein is the major virulence antigen of group A streptococci. Strains rich in this protein are resistant to phagocytosis by polymorphonuclear leukocytes, multiply rapidly in fresh human blood, and are capable of initiating disease. Strains lacking M protein are avirulent.[7] Group A streptococci may be divided into serotypes on the basis of antigenic differences in M-protein molecules. Over 80 such serotypes are currently recognized. Acquired human immunity to streptococcal infection is based on the development of opsonic antibodies directed against the antiphagocytic moiety of M protein. Such immunity is type specific and quite durable, lasting for many years and perhaps indefinitely. In some instances, cross-protection by antibody to one type against organisms of a heterologous type has been demonstrated.

The M-protein molecule penetrates the cell wall; this configuration localizes the type-specific moiety on the tips of hair-like fibrils protruding from the cell surface (Fig. 2). The manner in which M protein exerts its antiphagocytic effect is under current investigation. The protein prevents interaction of the streptococcal cell with complement components,[9] an effect that is enhanced by the ability of M protein to precipitate fibrinogen directly onto the bacterial surface.[10] This protective effect is nullified by the presence of adequate concentrations of type-specific antibody.

In addition to unique type-specific antigens, the M-protein molecule also contains common antigens (non-type-specific M antigens [NTSM], M-associated protein antigens [MAP]) shared by a wide variety of different M serotypes. Another protein antigen very closely associated with the M-protein molecule is the so-called serum opacity factor (OF). This factor is an α-lipoproteinase, which is detected by its ability to opacify horse serum. Strains of 16 of the currently identified M types are OF-positive, but the rest do not elaborate this antigen. All strains of OF-positive serotypes produce this substance, and OF is readily demonstrated in such strains even if they should lose their ability to produce detectable amounts of M protein. OF itself is antigenic and type specific, that is, its ability to opacify serum can be specifically inhibited by antiserum raised against homologous but not heterologous M types. This substance is of importance for two reasons. First, it is a useful epidemiologic marker that assists in classifying streptococci even when they are not identifiable by M type. Second, type-specific and non-type-specific immune responses to streptococcal M protein are generally weaker after pharyngeal infection with OF-positive than with OF-negative serotypes.[7]

Many group A streptococcal strains cannot be serotyped by precipitin reactions using anti-M sera, either because they lack detectable M protein or because they belong to undesignated types for which antisera are not available. The latter situation pertains particularly in the case of many of the strains associated with pyoderma. Non-M-typable strains may frequently be identified by a subsidiary typing system using slide agglutination reactions and based on antigenic differences in T proteins. While T protein has proved to be a useful epidemiologic marker, it has no known role in streptococcal virulence.

Another cell wall constituent, lipoteichoic acid (LTA), is an important virulence factor in group A streptococci. This substance, which has a marked affinity for binding to biologic membranes, is responsible for the first step in colonization, namely, adherence of *S. pyogenes* to fibronectin on the surface of a human epithelial cell.[11] A recently characterized cell-bound peptidase cleaves the C5a component of complement and inhibits neutrophil chemotaxis in vitro and in vivo.[12]

Extracellular Products

During the course of growth in vitro or in vivo, group A streptococci elaborate numerous extracellular products, only a limited number of which have been well characterized. Streptococcal pyrogenic exotoxin, formerly known as erythrogenic toxin, is responsible for the rash of scarlet fever. Experimentally, this substance exhibits a variety of other toxic properties including pyrogenicity, cytotoxicity, and enhancement of susceptibility to the lethal effects of endotoxin. Toxin production is induced by lysogeny with a temperate bacteriophage. There are three serologically distinct toxins (A–C), the effects of which may be neutralized by antibody.

Two distinct hemolysins are elaborated. Streptolysin O derives its name from its oxygen lability. It is reversibly inhibited by oxygen and irreversibly inhibited by cholesterol. In addition to its effect on erythrocytes, it is toxic to a variety of cells and cell fractions including polymorphonuclear leukocytes, platelets, tissue culture cells, lysosomes, and isolated mammalian and amphibian hearts. Streptolysin O is produced by almost all strains of *S. pyogenes* (as well as many group C and G organisms) and is antigenic. Measurement of ASO antibodies in human sera has proved exceedingly useful as an indicator of recent streptococcal infection.

Streptolysin S is a hemolysin produced by streptococci growing in the presence of serum (hence the "S") or in the presence of a variety of other substances such as serum albumin, α-lipoprotein, ribonucleic acid, or detergents such as Tween. Streptolysin S is nonantigenic, or at least no antibody to it has been detected that will neutralize its hemolytic activity. Streptolysin S shares with streptolysin O the capacity to damage the membranes of polymorphonuclear leukocytes, platelets, and sub-

cellular organelles. Unlike streptolysin O, it is not inactivated by oxygen, but it is quite thermolabile. Most strains of *S. pyogenes* produce both hemolysins. Hemolysis on the surface of blood agar plates is due primarily to streptolysin S, whereas streptolysin O exerts its hemolytic effect best in subsurface colonies (Fig. 1, Chapter 175), in pour plates, or in anaerobic cultures. An occasional strain may produce only one of the two hemolysins. Rarely, strains are encountered that lack both hemolysins.

Several extracellular products may, theoretically, serve to facilitate the liquefaction of pus and the spreading of streptococci through tissue planes. These include (*1*) four antigenically distinct enzymes that participate in the degradation of deoxyribonucleic acid (DNases A, B, C, and D); (*2*) hyaluronidase, which enzymatically degrades hyaluronic acid found in the ground substance of connective tissue; and (*3*) streptokinase, which promotes the dissolution of clots by catalyzing the conversion of plasminogen to plasmin. Still other known extracellular products are nicotinamide adenine dinucleotidase (NADase), proteinase, amylase, and esterase. Most of the substances just enumerated are antigenic. Antibodies to five of the extracellular products have been used in the serodiagnosis of streptococcal infection. These are ASO, anti-DNase B, antihyaluronidase, anti-NADase, and antistreptokinase.

The two most frequent clinical manifestations of streptococcal infection, pharyngitis and pyoderma, differ markedly in their epidemiologic, clinical, and bacteriologic characteristics.[13] Therefore, they are discussed separately.

STREPTOCOCCAL PHARYNGITIS

Epidemiology

Streptococcal sore throat is among the most common bacterial infections of childhood. Group A streptococci are responsible for the great majority of such infections, but strains of other serogroups, especially groups C and G, may be occasionally involved. The disease occurs primarily among children 5–15 years of age, with the peak incidence occurring during the first few years of school. All age groups are susceptible, however, and severe epidemics are common in military training facilities. There is no sex predilection. The disease is ordinarily spread by direct person-to-person contact, most likely via droplets of saliva or nasal secretions. Crowding such as occurs in schools or barracks favors interpersonal spread of the organism (Fig. 3) and may also enhance its virulence by processes of natural selection analagous to those that occur during mouse passage in the laboratory. The effect of crowding in facilitating transmission may account in part for the increased incidence of streptococcal pharyngitis in northern latitudes during the colder months of the year.

Explosive food- or water-borne outbreaks are also well documented. Contamination of dust, clothing, blankets, or other fomites does not play a significant role in contagion.

Group A streptococci frequently colonize the throats of asymptomatic persons. Pharyngeal carriage rates among normal schoolchildren vary with geographic location and season of the year. Carriage rates of 15–20 percent have been noted in several studies. The carriage rate among adults is considerably lower.

Studies of experimentally induced human infections and of transmission within military barracks have shed considerable light on the variables involved in interpersonal spread. During the acute phase of tonsillopharyngeal infection, M-typable group A streptococci are frequently present in large numbers in both the nose and throat. In untreated infections, organisms may persist for many weeks, although the signs and symptoms of illness abate within a few days. During convalescence, the organisms decrease in numbers, and they tend to disappear from the anterior nares sooner than from the throat. In addition, the M-protein content and virulence of persisting organisms gradually decline. The result of these qualitative and quantitative changes is that convalescent carriers are much less likely to transmit the organism to close contacts than are acutely infected persons (Fig. 4).

In patients who do not receive effective antibiotic therapy, type-specific antibodies are frequently detectable in the serum between 4 and 8 weeks after the infection. These opsonic antibodies protect against subsequent infection with organisms of the same M type, but the person remains susceptible to infection by heterologous types. Prompt and effective antibiotic therapy ablates the type-specific immune response.

Clinical Manifestations

The usual incubation period of streptococcal pharyngitis is 2–4 days. The onset of illness is heralded by the rather abrupt onset of sore throat accompanied by malaise, feverishness, and headache. Nausea, vomiting, and abdominal pain are common in children. Prominent physical findings include redness, edema, and lymphoid hyperplasia of the posterior portion of the pharynx; enlarged, hyperemic tonsils studded with grayish white exudate; enlarged, *tender* lymph nodes at the angles of the mandibles; and a temperature of 101°F or higher. In the absence of the aforementioned symptoms and signs, simple coryza, hoarseness, cough, or conjunctivitis do not suggest the

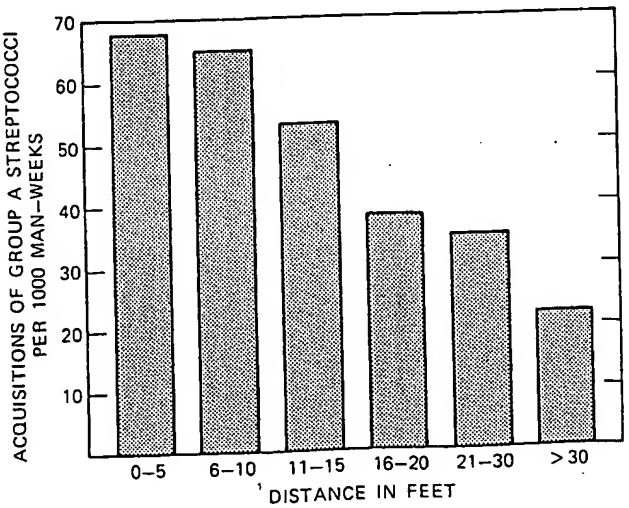

FIG. 3. Transmission of group A streptococci in a military barracks according to bed distance from the nearest carrier. (From Wannamaker,[4] with permission.)

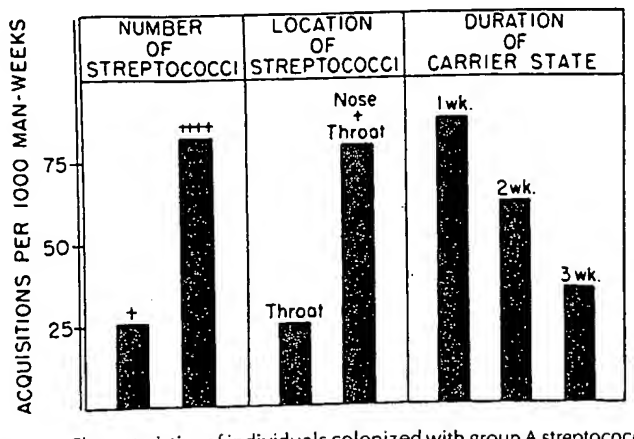

FIG. 4. Characteristics of individuals colonized with group A streptococci that influence communicability. Data were obtained in studies of military recruit populations. (From Rammelkamp,[3] with permission.)

presence of streptococcal infection. Laboratory findings include a positive throat culture for β-hemolytic streptococci and a total white blood cell count usually exceeding 12,000/mm^3 with increased numbers of polymorphonuclear leukocytes. The test for C-reactive protein is usually positive.

Not all patients with streptococcal pharyngitis have the full-blown syndrome just described. Endemically occurring infections in open populations manifest a wide spectrum of clinical severity. For example, only about half such patients with sore throats and positive throat cultures will have tonsillar or pharyngeal exudates. Patients who have undergone tonsillectomy tend to experience a milder clinical syndrome. In infants, the response to streptococcal infection is much less sharply focalized to the lymphoid tissue of the faucial and posterior pharyngeal area. Rhinorrhea, suppurative complications, low-grade fever, and a more protracted course tend to characterize infections at this age. Exudative pharyngitis in children less than 3 years of age is rarely streptococcal in etiology.

In the absence of suppurative complications, the disease is self-limited. Fever abates within 3–5 days. Virtually all acute signs and symptoms subside within a week, although several additional weeks may be required for tonsils and lymph nodes to return to their usual size. Penicillin shortens the period of fever and toxicity. Given the rather brief time course of untreated disease, however, such shortening of the clinical syndrome may not be striking unless therapy is initiated within the first 24 hours of illness.

Scarlet Fever. Scarlet fever results from infection with a streptococcal strain that elaborates streptococcal pyrogenic exotoxin (erythrogenic toxin). Although this disease is usually associated with pharyngeal infections, it may follow streptococcal infections at other sites such as wound infections or puerperal sepsis. Toxin production is dependent on lysogeny of the infecting streptococcus by a temperate bacteriophage. The clinical syndrome is similar in most respects to that associated with nontoxigenic strains, save for the scarlatinal rash. The latter must be differentiated from viral exanthems, drug eruptions, and particularly the rashes of toxic shock syndrome and Kawasaki disease.

The rash usually appears on the second day of clinical illness as a diffuse red blush with many points of deeper red that blanches on pressure. It is often first noted over the upper part of the chest and then spreads to the remainder of the trunk, neck, and extremities. The palms, soles, and usually the face are spared. Intradermal injection of scarlet fever antitoxin specifically neutralizes the toxin and causes blanching of the rash. This procedure (Schultz-Charlton reaction) is not used for diagnosis at the present time. Skin folds in the neck, axillae, groin, elbows, and knees appear as lines of deeper red (Pastia's lines). There are scattered petechiae, and the Rumpel-Leeds test of capillary fragility is positive. Occlusion of sweat glands imparts a sandpaper texture to the skin, a particularly helpful finding in dark-skinned patients.

The face appears flushed except for marked circumoral pallor. In addition to findings of exudative pharyngitis and tonsillitis, patients display an enanthem characterized by small, red, hemorrhagic spots on the hard and soft palate. The tongue is initially covered with a yellowish white coat through which may be seen the red papillae ("white strawberry tongue"). Later the coating disappears, and the tongue is beefy red in appearance ("red strawberry tongue"). The skin rash fades over the course of a week and is followed by extensive desquamation lasting for several weeks. A modest eosinophilia may be present early in the course of the illness, especially in cases in which both the rash and constitutional symptoms are slight.

Severe forms of scarlet fever, either associated with local and hematogenous spread of the organism (septic scarlet fever) or with profound toxemia (toxic scarlet fever), are characterized by high fever and marked systemic toxicity. The course may be complicated by arthritis, jaundice, and very rarely, hydrops of the gallbladder. Such severe forms of the disease are quite infrequent in the antibiotic era.

Intracutaneous administration of erythrogenic toxin in humans elicits local erythema (positive Dick test). No reaction occurs in persons with acquired immunity to the toxin. This test is not used clinically at the present time.

Recent reports have suggested the existence of a toxic shock-like syndrome due to *Streptococcus pyogenes*. The cases have occurred in adults, and in several instances the focus of infection has been a localized cellulitis or soft tissue infection. Patients have manifested a diffuse erythroderma, hypotension, mental status changes, and dysfunction of multiple organs including kidneys, liver, lungs, and heart.[14] The recent demonstration of an amino acid homology of nearly 50 percent between streptococcal pyrogenic exotoxin A and staphylococcal enterotoxin B, a putative mediator of nonmenstrual toxic shock syndrome, may explain the similarities in the syndromes caused by the two organisms.

Suppurative Complications. Inflammation in the faucial area induced by acute streptococcal infection may give rise to peritonsillar cellulitis, peritonsillar abscess, or retropharyngeal abscess. The abscesses themselves, however, frequently contain a variety of other oral flora including oral anaerobes, with or without group A streptococci. Direct extension of streptococci into adjacent structures may give rise to acute otitis media or acute sinusitis, which are among the most common suppurative complications of streptococcal pharyngitis. Suppurative cervical lymphadenitis may also occur. Extension up the cribriform plate of the ethmoid or via the mastoid bone may cause meningitis, brain abscess, or thrombosis of the intracranial venous sinuses. Streptococcal pneumonia, another potential suppurative complication, is discussed later.

Finally, bacteremic spread of the streptococci may result in a variety of metastatic foci of infection, for example, suppurative arthritis, endocarditis, meningitis or brain abscess, osteomyelitis, liver abscess, and so forth. Such complications are extremely rare since the advent of effective chemotherapy.

Nonsuppurative Complications. Nonsuppurative complications of streptococcal pharyngitis, ARF and AGN, are discussed in Chapter 177. The role of streptococci vis-à-vis other infectious and noninfectious agents in initiating certain other acute inflammatory disorders such as erythema nodosum and anaphylactoid purpura remains unresolved.

Diagnosis

Pharyngitis and tonsillitis may be due to a variety of infectious agents other than *Streptococcus pyogenes* (Chapter 43). *Corynebacterium diphtheriae*, the other major bacterial pathogen associated with exudative pharyngitis, is rare now, and when it occurs in classic form, it is differentiated by the appearance of the diphtheritic membrane, respiratory embarrassment, severe systemic toxicity, and myocardial and neurologic manifestations. Other bacterial agents such as *Neisseria gonorrhoeae* and, perhaps. *Neisseria meningitidis* may occasionally cause pharyngitis, as may *Mycoplasma pneumoniae*. Pharyngitis due to oral anaerobes (Vincent's angina) is characterized by a membranous exudate, fetid breath, and oral ulcerations. Fever and constitutional symptoms are not prominent.

Pharyngitis due to *Corynebacterium haemolyticum*, although rare, may closely mimic that due to *S. pyogenes*.[15] *Corynebacterium haemolyticum* affects primarily teenagers and young adults, and a high percentage of the patients have exudative pharyngitis and a scarlatiniform rash. The organism is more readily identified on rabbit or human blood agar than on sheep blood agar. Although detailed studies of therapy have not been carried out, *C. haemolyticum* pharyngitis appears to respond

to benzathine penicillin G or oral erythromycin. Another rare cause of acute pharyngitis is *Yersinia enterocolitica*.[16] Patients infected with this organism may appear quite ill and may or may not have associated enteric symptoms. When *Y. enterocolitica* pharyngitis is associated with disseminated yersinosis, the mortality may be appreciable. Diagnosis depends upon clinical clues because the organism is unlikely to be detected on routine throat cultures and antistreptococcal therapy is unavailing (see Chapter 207).

Most throat infections are viral in etiology. Infectious mononucleosis and adenovirus infections frequently give rise to exudative pharyngitis and thus may closely mimic streptococcal sore throat. Even when careful microbiologic techniques are used to detect bacteria, *Mycoplasma*, and viruses, no etiologic agent can be detected in approximately one-half of all cases of acute sore throat.[17]

Approximately one–quarter to one-third of all children complaining of sore throat have a positive throat culture for group A streptococci. Of these, about one-half can be demonstrated to have immunologically significant infection, as judged by a significant rise in serum titer of one or more antistreptococcal antibodies. Most of the remainder probably represent asymptomatic carriers since the average carriage rate among school-age children during the winter months is approximately 15 percent. Such asymptomatic carriers are at no risk of developing suppurative or nonsuppurative complications and do not require antibiotic therapy. Thus, on the average, about 15 of every 100 children and adolescents with acute pharyngitis require treatment for streptococcal sore throat.

Numerous studies have tested the precision with which physicians may differentiate between streptococcal and nonstreptococcal sore throat by clinical criteria alone. In the presence of a scarlatinal rash or during a documented epidemic of streptococcal infections, such differentiation is easy. On the other hand, in the case of endemically occurring infections the problem is much more complex. Certain clinical findings, particularly tonsillopharyngeal exudate and *tender*, enlarged lymph nodes at the angles of the jaws, have a statistically significant correlation with the presence of positive throat cultures for group A streptococci.[18] Such findings are not diagnostic, however. For instance, only one-half of the patients with immunologically proven streptococcal sore throat have tonsillar exudate; conversely, one-half to three-quarters of all cases of exudative pharyngitis are nonstreptococcal in etiology. This percentage is even higher in children less than 3 years of age.

In two separate studies the presence of a positive throat culture was accurately predicted on clinical grounds alone in 55 percent and 75 percent of cases, respectively, while a negative throat culture was correctly predicted in 73 and 77 percent of cases.[19,20] Thus, even highly experienced clinicians using clinical impressions alone would fail to treat one-quarter to one-half of the patients with positive throat cultures and would needlessly treat one in four of the large number of persons who are neither infected nor colonized by group A streptococci. Algorithms using specific epidemiologic and clinical data have been devised to enhance the examiner's "batting average," but these remain less accurate than the culture.

For this reason, throat culture remains the preferred method for diagnosing streptococcal pharyngitis. Failure to isolate β-hemolytic streptococci in a carefully obtained and accurately interpreted throat culutre rules out the diagnosis of streptococcal sore throat for practical purposes. It is true that approximately 10 percent of negative throat cultures are weakly positive on reculture. While the significance of these false-negative cultures cannot be ascertained in a given patient, the phenomenon should not be a cause for undue concern. Most such cultures likely reflect streptococcal carriage rather than acute streptococcal infection. In cases where doubt exists as to the validity of a negative culture, it is usually preferable to repeat the culture than to treat empirically with antimicrobial agents.

While a negative culture eliminates the necessity for therapy, a positive culture does not differentiate between acute infection and asymptomatic carriage. Serum antibody titers do not rise until convalescence and are thus of no help in short-term management. Although the degree of positivity of the throat culture may assist in making this differentiation, it is best to assume that all positive cultures in patients with acute pharyngitis are significant and to treat accordingly, while recognizing that, even with the use of the throat culture, some degree of overtreatment is inevitable.

Detailed instructions for obtaining and processing a throat culture have been published by the American Heart Association.[21] Under direct visualization with good illumination, the cotton or Dacron swab should be rubbed over both tonsils, or tonsillar fossae, the oropharynx, and the nasopharynx posterior to the uvula. Care should be taken to avoid the tongue and buccal mucosa. After culturing, the swab should be rolled over a portion of the surface of a blood agar plate, and the inoculated plate should be streaked with a wire loop in a manner that will yield isolated colonies. A stab is made through the agar with the inoculation loop to permit subsurface growth. This allows observation of hemolysis due to the action of streptolysin O, which is oxygen labile.

Sheep blood agar is preferred because clear-cut patterns of hemolysis are obtained on this medium and because sheep blood inhibits the growth of *Haemophilus haemolyticus*, colonies of which appear similar to β-hemolytic streptococci on blood agar plates. Human blood from a blood bank is less desirable because the presence of type-specific antibodies, ASO antibodies, antibiotics, or high concentrations of citrate may inhibit the growth of streptococci or the expression of β-hemolysis. In regard to isolation of group A streptococci, there is controversy in the literature as to the relative merits of plain sheep blood agar plates vs. plates to which trimethoprim and sulfamethoxazole have been added to suppress competing normal pharyngeal flora. Similar controversy exists as to the optimal atmosphere of incubation: aerobic, aerobic in the presence of 5–10% carbon dioxide, or anaerobic.[22] If blood agar plates are not immediately available, the swab may be placed in a dry sterile tube for transportation to the laboratory. After overnight incubation at 35–37°C, culture plates from patients with streptococcal pharyngitis will show colonies surrounded by clear zones of hemolysis as well as β-hemolysis around the agar stab. Plates that are negative on first reading should be reexamined after an additional 24 hours of incubation. Serologic grouping of β-hemolytic streptococcal isolates may now be readily performed by using commercially available kits. A less expensive and highly serviceable screening procedure, the bacitracin sensitivity test, may be performed once the organism has been isolated in pure culture. This susceptibility procedure is based on the observation that greater than 95 percent of all group A streptococcal strains are inhibited by low-potency (0.04 units) bacitracin disks, while 80–90 percent of non-group A strains are resistant. Since no group A streptococci resistant to penicillin have yet been described, antibiotic testing is unnecessary if this drug is to be used. The same might be said for erythromycin since group A streptococci resistant to this drug are extremely rare in the United States at this time. The prevalence of erythromycin-resistant strains of *S. pyogenes* is higher in certain other parts of the world.[23]

Fluorescent antibody techniques provide excellent results and specifically identify group A organisms. No quantitative information is gained as to the degree of positivity of the culture. A variety of commercial kits are now available that use antibodies for the rapid detection of group A carbohydrate antigen directly from throat swabs. Indicator systems employed are latex agglutination or enzyme immunoassay, and the tests can be completed in a matter of minutes. Results obtained with the best of these kits are highly specific, so a positive reaction obviates the need for a throat culture. Unfortunately, the kits are

somewhat less sensitive than are throat cultures,[22] and, therefore, immunologic tests may be negative in cases in which the conventional culture yields only a few streptococcal colonies. For this reason, physicians electing to use direct antigen tests should confirm negative test responses with a routine throat culture. This caveat applies with special force to epidemiologic settings in which the risk of acute rheumatic fever is appreciable (see Chapter 177).

Therapy

Therapy is directed toward the prevention of acute rheumatic fever and suppurative complications such as otitis media and acute sinusitis. Data on the preventability of poststreptococcal glomerulonephritis are less clear-cut. The drug of choice in the treatment of streptococcal infection is penicillin because its efficacy in the prevention of rheumatic fever is well established. Broader-spectrum, more expensive antibiotics such as ampicillin or amoxicillin are unnecessary.

Prevention of acute rheumatic fever requires eradication of the infecting streptococcus from the pharynx, an effect that depends on prolonged rather than high-dose penicillin therapy. This objective is efficientliy accomplished by the administration of a single injection of 1.2 million units of penicillin G benzathine. For children weighing less than 60 pounds, the dose is reduced to 600,000 units.[24] Many physicians elect to administer oral therapy. In this case, penicillin V, 250 mg three times a day, must be continued for a full 10 days. Even compliant patients, however, frequently find it difficult to remember to take the full course of oral therapy once they become asymptomatic.

In penicillin-allergic patients, erythromycin is the therapy of choice. Specific dosages vary somewhat with the preparation chosen but are in the range of 20–40 mg/kg/day divided into two to four equal doses, with the maximum daily dosage being 1 g. While twice-daily dosage appears satisfactory in children, data are lacking as to the efficacy of this dosage schedule in adults. Oral cephalosporins are effective in the treatment of streptococcal pharyngitis. They are useful in the penicillin-allergic patient whose allergy is not of the immediate type and who cannot tolerate oral erythromycin. The physician should bear in mind the possibility of an increased risk of allergic reactions to cephalosporins when treating penicillin-allergic patients.

Because tetracycline-resistant group A streptococci are prevalent in many areas, this drug is not recommended. Sulfonamides, which are highly effective in prophylaxis, are ineffective in the eradication of pharyngeal organisms or in the prevention of rheumatic fever when used as therapy for acute pharyngeal infections.

Treatment of group A streptococcal sore throat as long as 9 days after onset is still effective in the prevention of rheumatic fever.[25] Thus, if the patient is seen early in the course of his illness, the delay in initiation of therapy occasioned by obtaining a positive throat culture is not ordinarily a matter of concern. In the minority of patients, however, who are severely ill or toxic at presentation or who have evidence of sinusitis or otitis, antimicrobial therapy may be started at the initial visit after a throat culture has been obtained. Such therapy will reduce the period of infectivity and, if started early, shorten the duration of the clinical illness.[26] If oral therapy is prescribed, the throat culture serves as a guide to the necessity of completion of a full 10-day course or, alternatively, of recalling the patient for an injection of penicillin G benzathine. As discussed earlier, patients with signs and symptoms of acute pharyngitis and a positive test (properly performed and interpreted) for group A carbohydrate antigen should receive appropriate antimicrobial therapy.

Patients with more severe suppurative infections such as those involving the mastoid or ethmoid may require larger doses of penicillin (e.g., 600,000 units of penicillin G procaine intramuscularly once or twice a day or intravenous therapy with penicillin G). When streptococcal upper respiratory infection is complicated by the development of abscesses associated with suppurative cervical adenitis or in the peritonsillar or retropharyngeal soft tissues, incision and drainage are required.

Two aspects of therapy remain subject to debate. The first relates to the necessity for retreatment of "treatment failures." A variable percentage of patients, ranging from 5 to 30 percent, is found to harbor group A streptococci in the pharynx after completion of a course of penicillin. The incidence of failure is generally reported to be greater after oral than intramuscular therapy. Since prevention of rheumatic fever appears to require eradication of the streptococcus from the pharynx, such treatment failures are of concern. The causes for post-treatment culture positivity are multiple and include failure of compliance with oral medication schedules, reinfection with the same or different streptococcal types in the home or school environment, or true treatment failure. In everyday practice, it is usually impossible to differentiate between these alternatives.

True treatment failure is defined as reisolation of the original infecting streptococcal serotype shortly after completion of a full course of antibiotic therapy. It is sometimes associated with symptomatic relapse. Treatment failure occurs more frequently when the subject is a streptococcal carrier than it does among acutely infected individuals.[27] Recent reports suggest that the rate of treatment failure with oral and parenteral penicillin may be increasing somewhat. Proposed explanations for this phenomenon include the presence of β-lactamase-producing bacteria in the throat.[28] and the occurrence of penicillin tolerance among certain strains of group A streptococci.

The need for reculture of the throat after a course of antistreptococcal therapy is currently a matter of debate because the benefit–cost ratio of such cultures continues to decline in parallel with the incidence of acute rheumatic fever in developed countries. Certainly such cultures should be undertaken in high-risk circumstances (e.g., if the patient or a family member has a history of rheumatic fever) or when symptoms compatible with streptococcal infection persist or recur. Since 1985, rheumatic fever outbreaks have been reported in several areas of the United States in both civilian and military populations (see Chapter 177). In such areas, the approach to streptococcal infection must be particularly rigorous, and serious consideration should be given to routine performance of post-treatment cultures. Reculture is otherwise optional. If reculture is undertaken, only a single retreatment course is warranted for patients who still harbor group A streptococci.

The presence of persistently but weakly positive throat cultures after repeated courses of antibiotic therapy in an otherwise asymptomatic patient is not a cause for alarm. Such persons are streptococcal carriers[27] who are not at inordinate risk of developing rheumatic fever or of spreading their infection to others. Their most frequent problem is anxiety produced by multiple medical consultations and procedures associated with the streptococcal colonization. In the rare event in which, for medical or psychological reasons, eradication of chronic streptococcal carriage becomes highly desirable, recent data suggest that a combination of penicillin plus rifampin may be efficacious.[29,30]

A second unresolved issue relates to the management of family contacts of patients with streptococcal sore throat. Streptococcal acquisition rates of 25 percent or greater have been recorded in family contacts. Certainly, family contacts with symptoms of upper respiratory infection should be cultured and treated appropriately if positive. Asymptomatic family contacts should also be cultured in high-risk circumstances, e.g., the presence of a person in the family who has had rheumatic fever or known cases of rheumatic fever or poststreptococcal glomerulonephritis occurring in the general area. In situations of lesser risk, routine culture of asymptomatic family contacts is not recommended.[24]

There is no firm evidence to suggest that tonsillectomy re-

duces the incidence of rheumatic fever, either in healthy persons or in persons who have had rheumatic fever and faithfully maintained continuous antibiotic prophylaxis. In certain patients with recurrent bouts of tonsillopharyngitis, however, tonsillectomy may decrease the frequency of incapacitating acute infections. This potential benefit must be balanced against the possibility that tonsillectomized persons may be more likely to experience mild or subclinical infections that go unattended.

ERYSIPELAS

Erysipelas is an acute inflammation of the skin, with marked involvement of cutaneous lymphatic vessels, that is caused by group A streptococci. Occasionally group C strains are responsible. The disease, which occurs primarily in infants and in persons over 30 years of age, has become much less common in recent years. Erysipelas most often involves the face (Fig. 5), and in such cases there is usually a history of preceding streptococcal sore throat, although the exact mode of spread to the skin is unknown. When erysipelas involves the trunk or extremities, it often occurs at the site of a surgical incision or wound.

Clinically, the cutaneous inflammation is accompanied by chills, fever, and marked toxicity. The cutaneous lesion begins as a localized area of erythema and swelling and then spreads rapidly with advancing red margins, which are raised and well demarcated from adjacent normal tissue. There is marked edema, often with bleb formation, and in facial erysipelas the eyes are frequently swollen shut. The lesion may demonstrate central resolution while continuing to extend on the periphery. Facial erysipelas most often resolves spontaneously in 4–10 days, whereas if untreated a lesion on the trunk or extremities may involve large areas of the body surface and terminate fatally. Treatment with penicillin is curative.

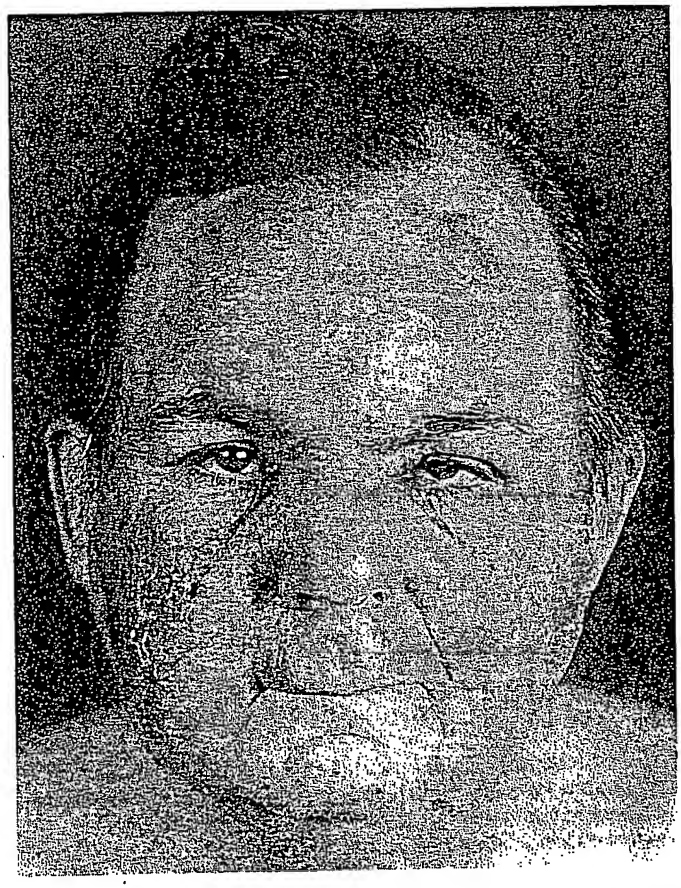

FIG. 5. Facial erysipelas. The lesion is well demarcated from surrounding skin and illustrates the typical "butterfly" distribution. (From Bisno,[31] with permission.)

STREPTOCOCCAL PYODERMA

Pyoderma is the term used collectively to denote localized purulent streptococcal infections of the skin. Some pyodermal lesions represent obvious secondary infections of wounds or burns. For the most part, however, the term is used synonymously with streptococcal impetigo or *impetigo contagiosa* to describe discrete purulent lesions that appear to be primary infections of the skin and that are extremely prevalent in many parts of the world.

Epidemiology

Pyoderma occurs most frequently among economically disadvantaged children dwelling in tropical or subtropical climates. It is also prevalent in northern climates during the summer months of the year in certain epidemiologic settings such as the American Indian reservations of Minnesota. The peak incidence of pyoderma is in children aged 2–5 years, as opposed to streptococcal pharyngitis, which occurs primarily in the 5- to 15-year-old age group. There is no sex predilection, and all races appear to be susceptible. The disease has been intensively studied, for example, among blacks in Mississippi and Alabama, American Indians in Minnesota, East Indians in Trinidad, and white military personnel in Vietnam.

The prevalence of pyoderma reaches extremely high levels in certain population groups. Among indigent black children attending Project Headstart classes during the summer in rural Mississippi, 40–50 percent were found to have identifiable pyodermal lesions in various stages of evolution. Eighty-five percent of children followed weekly throughout the summer had bacteriologically proven streptococcal impetigo[32]; most of these had multiple lesions. Recent reports from the United States and Europe have documented outbreaks of streptococcal pyoderma among workers in meat-packing plants who suffer numerous cutaneous cuts and abrasions.[33]

The prevalence of streptococcal pyoderma is markedly influenced by several factors, the most important of which appear to be climate and level of hygiene. Studies among Colombian school children[34] showed the lowest prevalence in Bogotà (8700 ft elevation, cool climate), intermediate prevalence in Medellin (5000 ft elevation, temperate climate), and highest incidence in Apartado (sea level, tropical climate). At each level of elevation, skin lesions were more frequent among persons with poor hygiene than among those with good hygiene (Fig. 6). Among Colombian military troops in the field, those conducting operations in humid tropical rain forests experienced a considerably greater incidence of pyoderma than those operating in the dry tropical savanna.

The mode of spread of streptococcal pyoderma is as yet poorly understood. Possible means of transmission include direct contact, environmental contamination, and arthropod vectors such as the *hippelates* fly, which has been shown to carry group A streptococci on its legs for periods of more than 24 hours.

Meticulous studies performed in children at Red Lake Indian Reservation, Minnesota[35] have demonstrated that the streptococci responsible for pyoderma initially colonize the unbroken skin, an observation that probably explains the influence of personal hygiene on disease incidence. Development of skin colonization with a given streptococcal type precedes the development of impetiginous lesions due to the same serotype by an average interval of 10 days (Fig. 7). The mechanism of production of skin lesions is unproved, but is most likely due to intradermal inoculation of surface organisms by abrasions, minor trauma, or insect bites. Lesions of scabies have also been

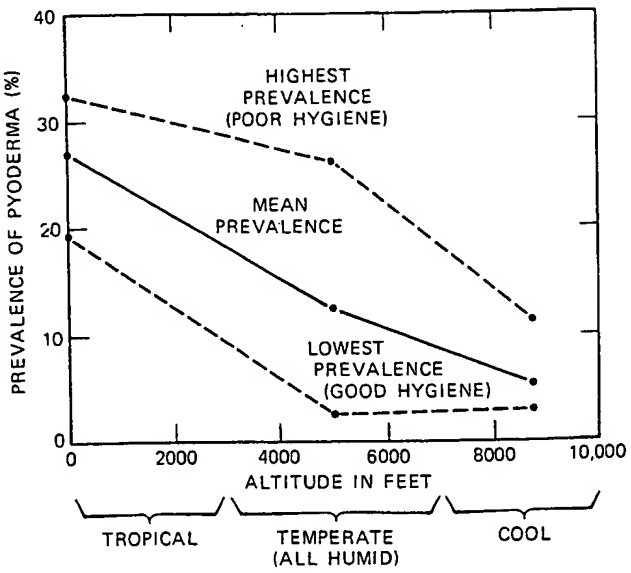

FIG. 6. Prevalence of pyoderma among lower socioeconomic class Colombian children in relation to altitude (climate) and level of hygiene. (From Taplin et al.,[34] with permission.)

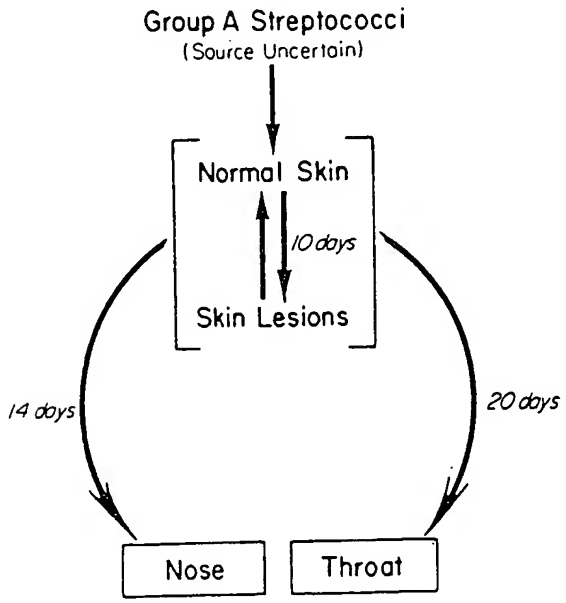

FIG. 7. Representative sequence of the spread of "pyoderma strains" of group A streptococci among different body sites. (From Ferrieri et al.,[35] with permission.)

demonstrated to harbor group A streptococci in Trinidad where epidemics of human scabies and of pyoderma-associated nephritis coexist. Frequently there is a transfer of the streptococcal strains from the skin and/or impetigo lesions to the upper respiratory tract. The interval between colonization of the skin and colonization of nose and/or throat averages 2–3 weeks (Fig. 7).

Bacteriologic Findings

Streptococci isolated from pyodermal lesions are primarily group A, but occasionally representatives of other serogroups such as C and G are responsible. Group A streptococci that cause impetigo differ in several respects from those usually associated with tonsillitis and pharyngitis. So-called skin strains belong to different M serotypes from the classic "throat strains"; since most have been identified in recent years, they tend to comprise the higher-numbered M types. There is a great multiplicity of M-protein types among the "skin strains," and many of these types have never been fully characterized and classified. As a result, many strains isolated from skin lesions are not typable with currently available batteries of M typing sera. Moreover, many pyodermal strains belong to "difficult" types that lose identifiable M protein rapidly on subculture in the laboratory and that are very weakly immunogenic in rabbits. Therefore, the M typing system is not entirely satisfactory for identifying "skin strains." This has led to increased use of the T-agglutination system. Unlike M protein, T antigen has no knnown biologic significance, but it is a stable, relatively easily measured epidemiologic marker by which the great majority of streptococcal strains can be categorized. Pyoderma streptococci are frequently not monotypic in their T typing reactions but tend to agglutinate several different typing sera, which gives rise to characteristic "pattern" reactions such as 3/13/B3264 and 8/25/imp 19. Each of these patterns may embrace several different M types, a fact that limits the utility of the T typing system at its current stage of development.

The well-known streptococcal M types that frequently give rise to exudative tonsillitis (e.g., types 1, 3, 5, 6, 12, 18, 19, 24, and others) are rarely found in skin lesions. On the other hand, as pointed out before, "skin strains" frequently colonize the throat. In populations in which pyoderma is hyperendemic, streptococcal carriage rates of 10–15 percent are seen during the warmer months, and most of these streptococci belong to "pyoderma" serotypes. For the most part, however, "skin strains" cause few or no symptoms when lodged in the throat. A relatively small number of serotypes seem capable of regularly initiating clinically apparent infection of both the skin and throat.[36]

Immunology

The ASO response after cutaneous streptococcal infection is weak. There is experimental evidence to suggest that this may be due to local inactivation of streptolysin O by skin lipids. Modest ASO responses are frequently observed when streptococcal pyoderma is accompanied by pharyngeal colonization. In contrast, the immune response to anti-DNase B is brisk; antihyaluronidase reactivity is also a useful test in the serodiagnosis of pyoderma.[37,38]

In uncomplicated pyoderma, type-specific opsonic antibodies are detectable 2–3 months after the development of infection. In one study[39] such antibodies were present in 12 percent of a small group of patients with pyoderma alone but in over half of the people who had concomitant pharyngeal carriage. In another study, type-specific antibodies were present in most patients convalescing from pyoderma-associated nephritis due to M type 55. It is not yet known whether such antibodies play a role in the prevention of reinfection analogous to that which has been established in pharyngeal infections. The existence of acquired immunity by whatever mechanism is suggested by the fact that, among American soldiers in Vietnam, pyoderma was more than 2.5 times as prevalent in whites as in blacks performing the same duties.

Clinical Manifestations

The lesion begins as a papule that rapidliy evolves into a vesicle surrounded by an area of erythema. The vesicular lesions are evanescent and rarely recognized clinically; they give rise to pustules that gradually enlarge and then break down over a period of 4–6 days to form characteristic thick crusts (Fig. 8). The lesions heal slowly and leave depigmented areas. A deeply ulcerated form of impetigo is known as *ecthyma*.

Streptococcal impetigo occurs on exposed areas of the body,

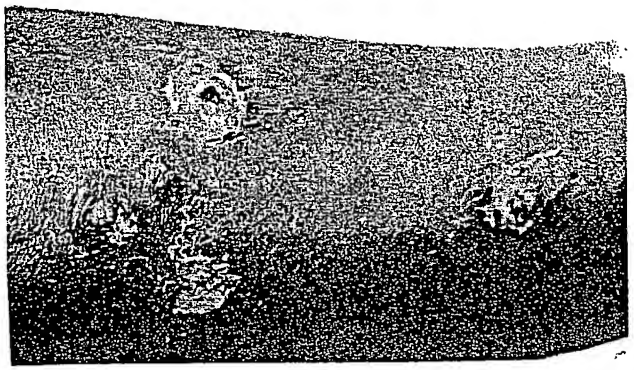

FIG. 8. Multiple pyoderma lesions on the lower extremities of rural Mississippi children. (Courtesy of Dr. K. Nelson, Baltimore, MD.)

most frequently on the lower extremities. The lesions remain well localized but are frequently multiple. Although regional lymphadenitis often occurs, systemic symptoms are not ordinarily present.

Adequate culture of crusted impetiginous lesions requires removal of the surface crusts and culture of the base of the lesions. If this is done, strongly positive cultures for group A streptococci are usually obtained, even from indolent-appearing lesions in later stages of healing. Staphylococci are often isolated as well but do not appear to be primary pathogens in this setting. The response to penicillin therapy is equally prompt whether or not the lesions contain penicillinase-producing staphylococci. Indeed, staphylococcal impetigo is a distinct entity that must be differentiated from that caused by *Streptococcus pyogenes*. Staphylococcal impetigo usually consists of bullous lesions that rupture and leave thin "varnishlike" crusts. Such bullae yield pure cultures of staphylococci, and often they are phage type 71.

Therapy and Prevention

Antibiotic treatment of streptococcal pyoderma is similar to that of pharyngitis. Intramuscular penicillin G benzathine, oral penicillin, or oral erythromycin all give excellent cure rates of 97 percent or higher. The exact duration of therapy is not firmly established; 10 days of treatment is advisable when oral regimens are used. Topical antibiotic or antiseptic preparations are much less effective and of course do not prevent the development of new lesions in untreated areas or terminate the frequently associated nasal and pharyngeal carrier state. A recent report indicating excellent clinical and bacteriologic results in clearing lesions with topical muciprocin awaits confirmation.[39a] Adherence to good regimens of personal hygiene, with special attention to frequent scrubbing with soap and water, is the most effective preventative measure currently available.

Complications

Although septicemia accompanies streptococcal impetigo on rare occasions, suppurative complications are on the whole most uncommon. For as yet unexplained reasons, rheumatic fever does not occur after streptococcal pyoderma (Chapter 177). On the other hand, cutaneous infections with nephritogenic strains of group A streptococci are the major antecedent of poststreptococcal glomerulonephritis in many areas of the world. There are as yet no conclusive data to indicate that treatment of an individual case of pyoderma will prevent the subsequent occurrence of nephritis in these patients. Such therapy is nevertheless important as an epidemiologic measure in eradicating nephritogenic strains from the environment.

OTHER STREPTOCOCCAL INFECTIONS

Streptococcal *cellulitis*, an acute, spreading inflammation of the skin and subcutaneous tissues, usually results from infection of burns or wounds. Recurrent episodes of cellulitis may occur in extremities in which lymphatic drainage has been impaired. Examples include patients with filariasis and women who have undergone radical mastectomy with axillary node dissection. Such episodes may be accompanied by high fever and prostration. Recurrent episodes of severe cellulitis have been reported in certain patients who have undergone coronary artery bypass grafts.[40] The cellulitis uniformly occurs in the extremity of the donor's saphenous vein, and patients with tinea pedis of the venectomy limb are particularly at risk.[41,42] Although pathogenic bacteria are difficult to recover during these episodes, the appearance of the lesions and the response to penicillin therapy suggest a streptococcal etiology. The few β-hemolytic streptococci that have been recovered and characterized belonged to serogroups other than group A.[43]

Lymphangitis may accompany cellulitis or may occur after clinically minor or inapparent skin infection. Lymphangitis is readily recognized by the presence of red, tender, linear streaks directed toward enlarged, tender regional lymph nodes. It is accompanied by systemic symptoms such as chills, fever, malaise, and headache. *Perianal cellulitis* or asymptomatic anal infection by group A streptococci has been the source of several reported outbreaks of hospital-acquired streptococcal infection. *Puerperal sepsis* follows abortion or delivery when streptococci colonizing the patient herself or transmitted from medical personnel invade the endometrium and surrounding structures, lymphatics, and blood stream. The resulting endometritis and septicemia may be complicated by pelvic cellulitis, septic pelvic thrombophlebitis, peritonitis, or pelvic abscess. This disease was associated with high mortality in the preantibiotic era. Although endocarditis due to *S. pyogenes* was relatively common in the preantibiotic era, it is now rarely seen.[44] Meningitis due to *S. pyogenes* usually follows upper respiratory infection and is indistinguishable clinically from other forms of acute pyogenic meningeal infection.[45]

Another rare but potentially life-threatening entity is streptococcal myositis.[46] It is characterized by severe pain and inflammation in the affected muscle, marked systemic toxicity, and elevated serum levels of creatine phosphokinase. Muscle compartment pressures may be elevated. Therapy includes aggressive surgical débridement and intravenous penicillin. Mortality in reported cases has been high. Streptococcal gangrene is discussed in Chapter 74.

Pneumonia due to *Streptococcus pyogenes* is now rare. When such cases do occur, they are frequently associated with preceding viral infections such as influenza, measles, or varicella or with chronic pulmonary disease. Numerous epidemics have been described in military recruit populations.[47] In one-third or fewer of the cases, there is a history of preceding streptococcal upper respiratory infection. The onset is typically abrupt, and the disease is characterized by chills, fever, dyspnea, cough productive of blood-streaked sputum, pleuritic chest pain, and in more severe cases, cyanosis. The pulmonary picture is that of bronchopneumonia with consolidation being uncommon. Empyema develops in 30–40 percent of the cases, tends to appear early in the disease, and typically consists of copious amounts of thin serosanguinous fluid. Bacteremia occurs in 10–15 percent of the cases. Complications include mediastinitis, pericarditis, pneumothorax, and bronchiectasis. Mortality is low with penicillin therapy and adequate drainage of empyema, but the clinical course of the disease is often prolonged.

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177. NONSUPPURATIVE POSTSTREPTOCOCCAL SEQUELAE: RHEUMATIC FEVER AND GLOMERULONEPHRITIS

ALAN L. BISNO

RHEUMATIC FEVER

Acute rheumatic fever (ARF) is a disease characterized by nonsuppurative inflammatory lesions involving primarily the heart, joints, subcutaneous tissues, and central nervous system. In its classic form, the disorder is acute, febrile, and largely self-limited. However, damage to heart valves may occur, and such damage may be chronic and progressive and lead to severe cardiac failure, total disability, and not infrequently, death many years after the acute attack. ARF is extremely variable in its manifestations; it remains, basically, a clinical syndrome for which no specific diagnostic test exists. Insofar as is known, all cases of ARF follow group A streptococcal upper respiratory tract infection, although the exact mechanisms mediating development of the disease remain speculative. Persons who have suffered an attack of ARF are particularly predisposed to recurrent episodes after subsequent group A streptococcal infections.

HISTORY

Guillaume de Baillou (1538–1616), also known as "Ballonius," first clearly distinguished acute arthritis from gout. Thomas Sydenham (1624–1689) described chorea but failed to associate this entity with other manifestations of ARF. Raymond Vieussens (1641–1715) published pathologic descriptions of mitral stenosis and aortic insufficiency. It remained, however, for William Charles Wells in 1812 to emphasize the association of rheu-